

### REMARKS

Claims 1-19, 21-23, 45 and 68 are pending in this application with claims 1, 23, 45, and 68 being independent claims. No new matter has been added.

### Specification

The paragraph at page 3, beginning at line 21 has been amended to correct a typographical error. The word "dose" was inadvertently typed as "does" in the application as filed. The amendment corrects this error.

Additionally, paragraphs on page 9-10 pertaining to figures 3, 4, 5, 8, 12 and 13 have been amended to reflect changes made to the drawing labels to address the Draftperson's Drawing Review.

### Rejections Under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1-19, 21-23, 45, and 68 under 35 U.S.C. §112, second paragraph as unclear. Applicants respectfully traverse the rejection.

The Examiner indicates that the meaning of the phrase "reduce the likelihood" is not clear. Applicants submit that the phrase means a statistical reduction the chance that a subject will acquire a streptococcal or staphylococcal infection. Page 22, lines 1-11 of the specification as filed describes methods to compare the acquisition of infection by test versus control subjects that have been exposed to streptococcal or staphylococcal bacteria. As described in the specification, a subject treated according to the claimed methods would be less likely to acquire a streptococcal infection than would a subject not treated according to the claimed methods.

Applicants respectfully submit that the meaning of the phrase "reduce the likelihood" is clear when read in the context of the specification. Thus, Applicants request the Examiner reconsider and withdraw the rejection of claims 1-19, 21-23, 45, and 68 under 35 U.S.C. §112, second paragraph.

### Rejections Under 35 U.S.C. §103

The Examiner rejected claims 1-19, 21-23, 45, and 68 under 35 U.S.C. §103(a) as being unpatentable over Yutaka (JP 6 107 550, published April 19, 1994). Applicants respectfully traverse the rejection.

To support a *prima facie* case for obviousness, the Examiner must demonstrate that the reference teaches all the limitations of the claim, there is a suggestion or motivation to modify the reference to make the claimed invention, and there is a reasonable expectation of success. Applicants respectfully submit that the Examiner has not met the necessary burden to support a *prima facie* case of obviousness for the following reasons.

Applicants submit that the Yutaka reference does not teach the limitations of the claimed invention. Claims 1-19, 21-23, 45, and 68 are drawn to methods of treating a subject to reduce the likelihood of a streptococcal or staphylococcal infection through the oral administration of an agent that binds to a hyaluronic acid-binding region of a CD44 protein in an amount effective to interfere with adhesion of streptococcal bacteria to CD44 protein in the subject and inhibit streptococcal or staphylococcal colonization of the pharynx. The claimed invention relates, in part, to methods to prevent or reduce the establishment of a streptococcal or staphylococcal infection in a subject who is likely to be exposed to, or is known to have been exposed to streptococcal or staphylococcal bacteria. Thus, the claimed methods relate to prophylactic treatment of subjects without symptoms of inflammation from streptococcal or staphylococcal infection. In contrast, the Yutaka reference generally relates to methods to heal inflammation, not methods to prevent infection. The Yutaka reference describes a method to administer hyaluronic acid composition to heal wounds and/or reduce inflammation (see Yutaka, paragraph [0009]), and suggests the administration of a hyaluronic acid composition as an anti-inflammatory to treat subjects with *existing* inflammation. The invention as claimed in the instant application, relates to the administration of agents to *prevent* the onset of infection, in subjects who do not have inflammation. The Yutaka does not teach the prophylactic administration of hyaluronic acid or any agent to inhibit colonization of the pharynx by streptococcal or staphylococcal bacteria and reduce the likelihood of the onset of an infection by streptococcal or staphylococcal bacteria. Thus, Applicants respectfully submit that Yutaka does not teach all limitations of the instant claims.

Applicants also submit that the Examiner has not identified motivation in the Yutaka reference or in the knowledge generally available to one of ordinary skill in the art to modify the teachings of Yutaka to make the claimed invention. The Yutaka reference describes methods to relieve inflammation by administering a hyaluronic acid composition that acts by “adhering to inflamed mucous membranes to stimulate exudation of healing substances and protect inflamed mucous membranes,” (see Yutaka, paragraph [0015]). Applicants assert that Yutaka’s disclosure of an anti-inflammatory agent that adheres to inflamed membrane and heals inflammation would not provide motivation for one of ordinary skill to administer the agent to a subject without inflammation. Applicants assert that one of ordinary skill in the art would not expect methods of reducing existing inflammation in a tissue to be useful for preventing the onset of a streptococcal or staphylococcal infection. Applicants respectfully submit that the motivation necessary to support a *prima facie* case of obviousness is absent.

Applicants also assert that based on the disclosure in the Yutaka reference, one of ordinary skill would have no expectation of success. The Yutaka reference suggests that hyaluronic acid “has no biological activity” and that hyaluronic acid is a “carrier of the wound-healing substances and anti-inflammatory substances that are biologically active” (Yutaka at paragraph [0003]). Applicants submit that one of ordinary skill in the art would have no reasonable expectation that administering hyaluronic acid, described by Yutaka as lacking activity, would be successful in reducing the likelihood of onset of a streptococcal or staphylococcal infection.

Applicants respectfully submit that the Examiner has not met the burden required to establish a *prima facie* case of obviousness based on the Yutaka reference. Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-19, 21-23, 45, and 68 under 35 U.S.C. §103(a).

The Examiner rejected claims 1-19, 21-23, 45, and 68 under 35 U.S.C. §103(a) as being unpatentable over Schrager et al. (J. Clin. Invest., Volume 98, Number 9, November 1996). Applicants respectfully traverse the rejection.

To make a *prima facie* case for obviousness, the Examiner must demonstrate that the reference teaches or suggests all the limitations of the claim, that there is a suggestion or

motivation to modify the reference to make the claimed invention, and that there is a reasonable expectation of success. Applicants respectfully submit that the Examiner has not met the requirements to support a *prima facie* case of obviousness.

Applicants submit that the Schrager et al. reference does not teach or suggest every claim limitation. Claims 1-19, 21-23, 45, and 68 relate to the treatment of a subject to reduce the likelihood of streptococcal or staphylococcal infection. The claimed methods include, in part, the oral administration of an agent that binds to a hyaluronic acid-binding region of a CD44 protein in an amount effective to interfere with adhesion of streptococcal bacteria to CD44 protein in the subject and inhibit streptococcal colonization of the pharynx. Applicants submit that the Schrager et al. reference discloses application of the monoclonal antibody IM7.8.1 to CD44 in *cultured* cells, and does not disclose administration of the antibody to a subject. Thus, Applicants submit that the reference does teach or suggest all the claim limitations.

The Examiner also contends that based on the disclosure of Schrager et al. "it would be expected that the IM7.8.1 antibody would be effective in a method of treatment against streptococcal and staphylococcal infections because the IM7.8.1 antibody prevents colonization of the pharynx." (Office Action at pages, 5-6). Applicants respectfully disagree with the Examiner's interpretation of the reference and assert that Schrager et al. does not provide any teaching with respect to *in vivo* bacterial colonization or the prevention thereof.

Applicants respectfully submit that one of ordinary skill in the art would know that *in vitro* methods are not simply transferable to *in vivo* applications. Applicants assert that even if one of ordinary skill in the art was motivated to try, there would be no reasonable expectation of success, in part because of features inherent in oral biology and biology of the pharynx. One such feature is the existence of a mucous layer over the pharynx, which would suggest to one of ordinary skill that an orally administered antibody would not have access to the desired pharyngeal target. Applicants submit that the disclosure of an antibody that inhibits binding of some strains of streptococcal bacteria to CD44 *in vitro*, would not provide one of ordinary skill in the art with a reasonable expectation that oral administration of an antibody would prevent streptococcal or staphylococcal infection in a subject.

Applicants respectfully assert that the Examiner has not met the requisite burden of establishing a *prima facie* case of obviousness and request the Examiner reconsider and

withdraw the rejection of claims 1-19, 21-23, 45, and 68 under 35 U.S.C. §103(a) as being unpatentable over Schrager et al.

The Examiner rejected claims 1-19, 21-23, 45, and 68 under 35 U.S.C. §103(a) as being unpatentable over Zheng et al. (The Journal of Cell Biology, vol. 130, No. 2, July 1995). Applicants respectfully traverse the rejection.

To make a *prima facie* case for obviousness, the Examiner must demonstrate that the reference teaches or suggests all the limitations of the claim, that there is a suggestion or motivation to modify the reference to make the claimed invention, and that there is a reasonable expectation of success. Applicants respectfully submit that the Examiner has not met the burden to support a *prima facie* case of obviousness.

Applicants submit that the Zheng et al. reference does not teach every claim limitation. Claims 1-19, 21-23, 45, and 68 relate to the treatment of a subject to reduce the likelihood of streptococcal or staphylococcal infection. The claimed methods include, in part, the oral administration of an agent that binds to a hyaluronic acid-binding region of a CD44 protein in an amount effective to interfere with adhesion of streptococcal bacteria to CD44 protein in the subject and inhibit streptococcal colonization of the pharynx. Applicants submit that the Zheng et al. reference discloses several antibodies that bind to CD44 in *cultured* cells, but Applicants assert that the reference does not teach or suggest administration of an antibody that binds to a hyaluronic acid-binding region of a CD44 protein to a subject to reduce the likelihood of streptococcal or staphylococcal infection. Thus, Applicants submit that the reference does teach or suggest all the claim limitations.

The Examiner suggests that Zheng et al. teaches a method of treating a subject to reduce the likelihood of streptococcal or staphylococcal infections because “monoclonal antibodies to CD44, for example KM114 has a high affinity for CD44 than its ligand and blocks binding to the CD44” (Office Action at page 6). Applicants respectfully disagree with the Examiner’s conclusion because Zheng et al. discloses only *in vitro* methods and results and does not teach or suggest the use of any methods for preventing streptococcal or staphylococcal infection in a subject. An *in vitro* method that is a scientific inquiry about ligand recognition function and functional domains of CD44, does not suggest or provide one of skill in the art a reasonable

expectation of success for a very specific treatment for a very specific organism. Applicants submit that the disclosure of high-affinity binding of an antibody to CD44 in culture does not teach or suggest to one of ordinary skill in the art that the antibody could be administered to a subject as an effective prophylactic treatment against streptococcal and staphylococcal infections or to reduce bacterial colonization in the pharynx.

The Examiner also suggests that “it would be expected, barring evidence to the contrary, that the antibodies taught by Zheng et al. would be effective in a method of treating against streptococcal and staphylococcal infections because the antibodies inhibit binding to CD44 and thereby prevent colonization of the pharynx.” (Office Action at page 7). Applicants respectfully assert that the Examiner does not provide a basis to support this conclusion, and disagree with the Examiner’s interpretation of the reference. The Zheng et al. reference does not provide any teaching with respect to *in vivo* colonization or the prevention thereof and, as argued above, *in vitro* methods are not simply transferable to *in vivo* applications. Thus, the disclosure of *in vitro* antibody binding in Zhang et al. would not provide a reasonable expectation of success of administering the antibody to a subject to reduce the subject’s likelihood of streptococcal or staphylococcal infection.


Applicants respectfully assert that the Examiner has not met the requisite burden of establishing a *prima facie* case of obviousness and request the Examiner reconsider and withdraw the rejection of claims 1-19, 21-23, 45, and 68 under 35 U.S.C. §103(a) as being unpatentable over Zheng et al.

**CONCLUSION**

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicants' representative at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, which is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,  
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Docket No. B0801.70237US00  
Date: January 30, 2004  
x01/30/04x



ocket No. B0801/7237; Entitled: Prevention a  
Treatment of Streptococcal and Staphylococcal  
Infection; Inventors: Wessels et al.

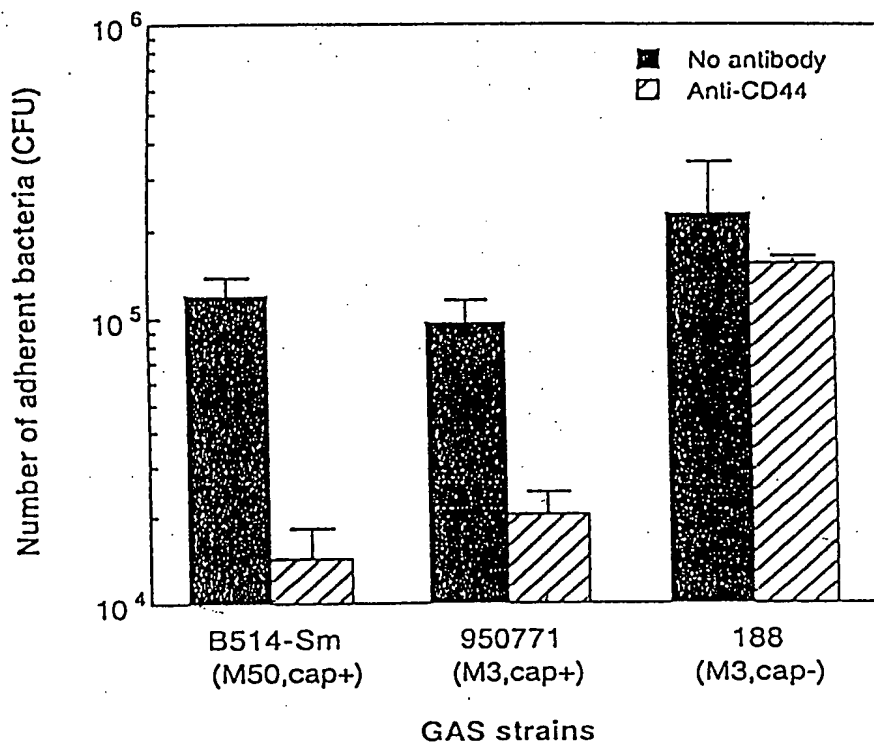


Fig. 1

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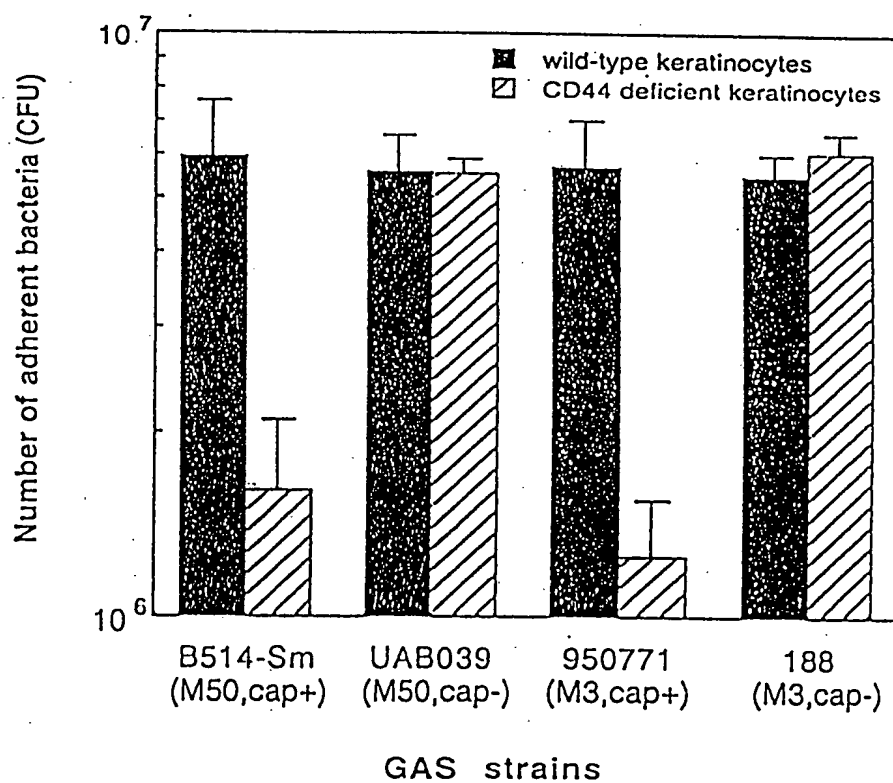


Fig. 2

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Percent of mice with positive throat culture

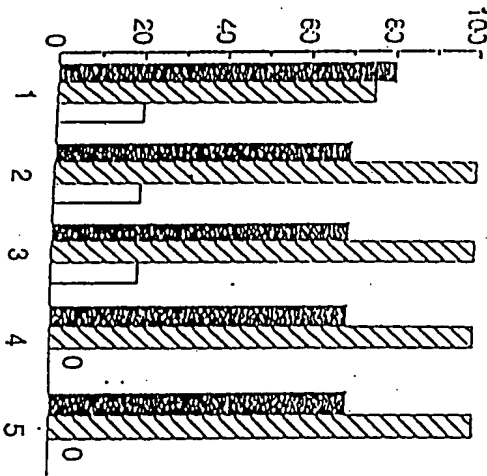
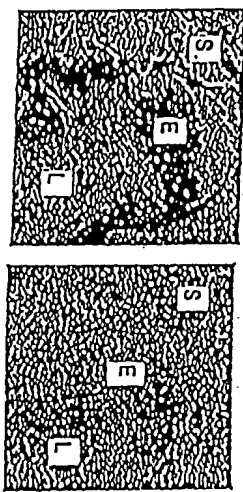


Fig. 3A

Fig. 3B



Days after inoculation

Fig. 3D

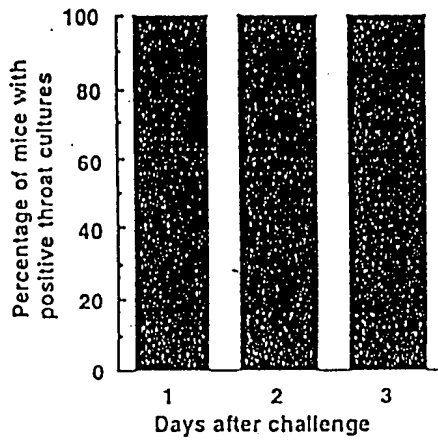
CD44 expression Histology Score (0-4)	Throat culture results				
	Day 1	Day 2	Day 3	Day 4	Day 5
Wild-type mice (n=10)					
4.0 (range 2.4-4.0)	8+	7+	7+	7+	7+
	2-	3-	3-	3-	3-
CD44-antigen mice (n=9)					
4.0	-	+	+	+	+
4.0	+	+	+	+	+
3.6	+	+	+	+	+
3.0	+	+	+	+	+
1.8	-	-	-	-	-
1.1	-	-	-	-	-
1.0	+	+	+	-	-
1.0	-	-	-	-	-
1.0	-	-	-	-	-

Fig. 3C

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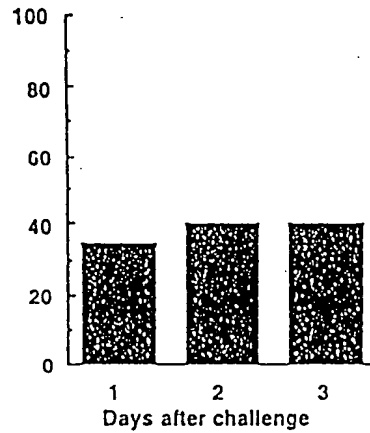


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mAb treatment: Control

**Fig. 4A**



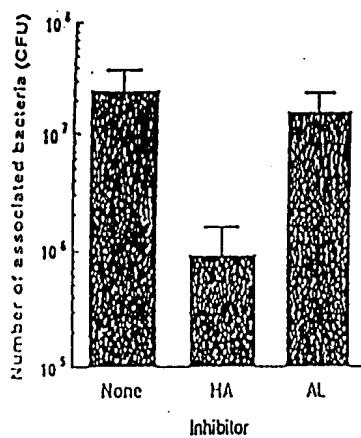
Anti-CD44

**Fig. 4B**

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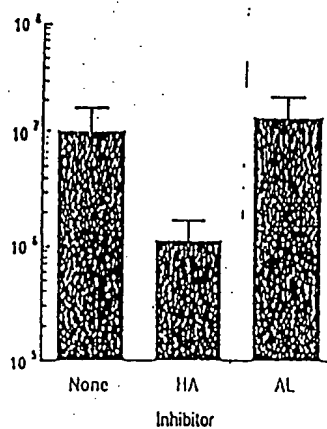


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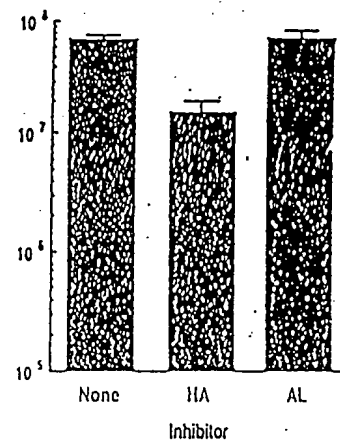
Time inhibitors added: 0 min

Fig. 5A



45 min

Fig. 5B



120 min

Fig. 5C

~~Figure 5~~

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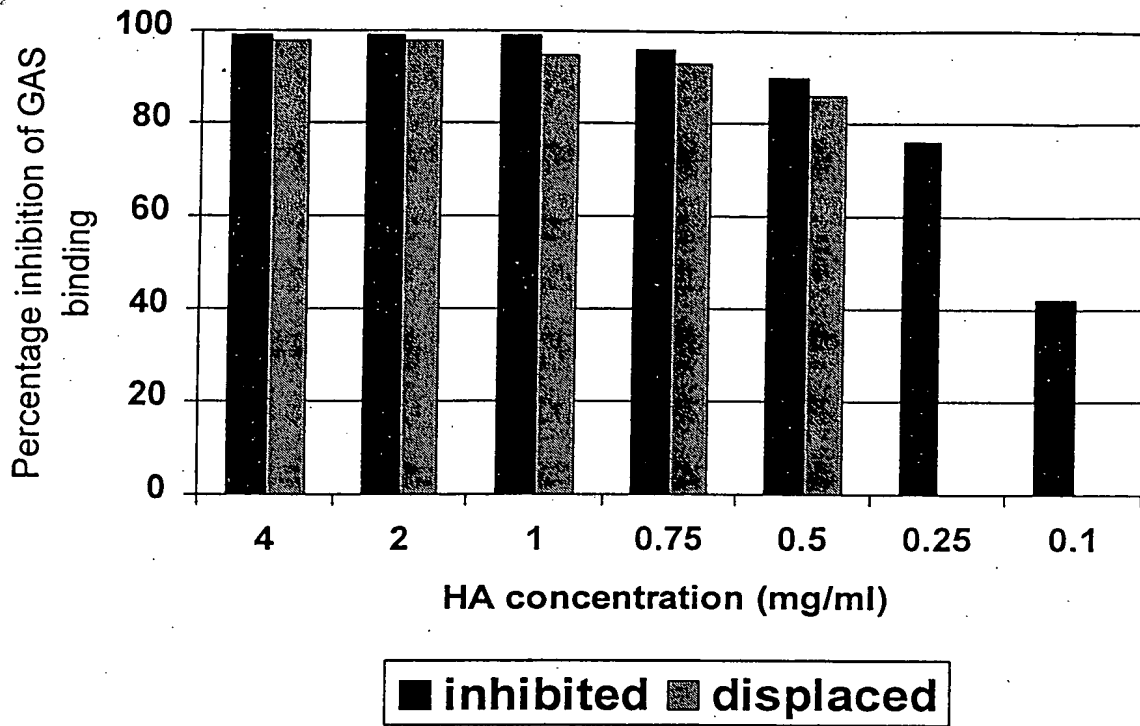


Fig. 6

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~~Figure 6~~



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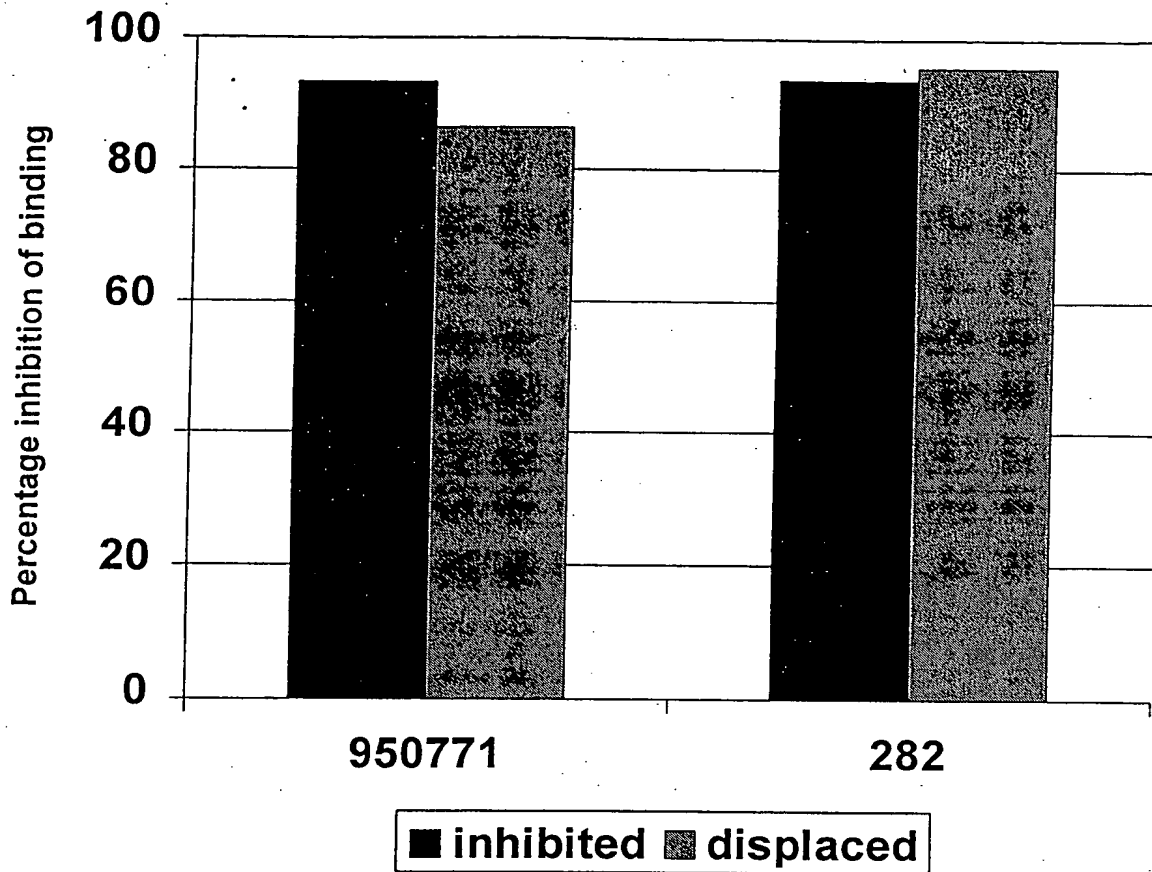


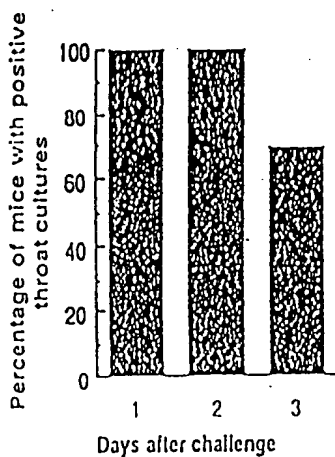
Fig. 7

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~~Figure 7~~

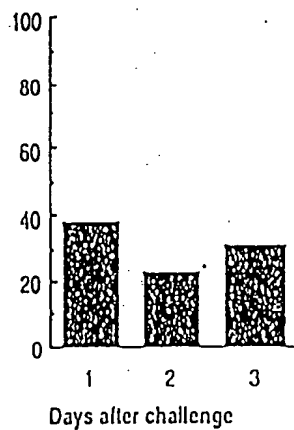


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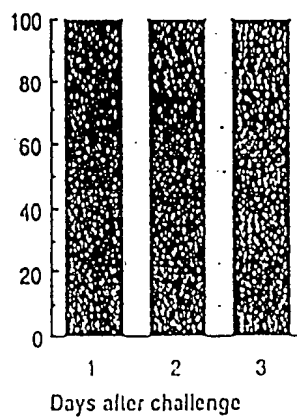
Pretreatment: Saline

Fig. 8A



HA

Fig. 8B



AL

Fig. 8C

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~~Figure 8~~



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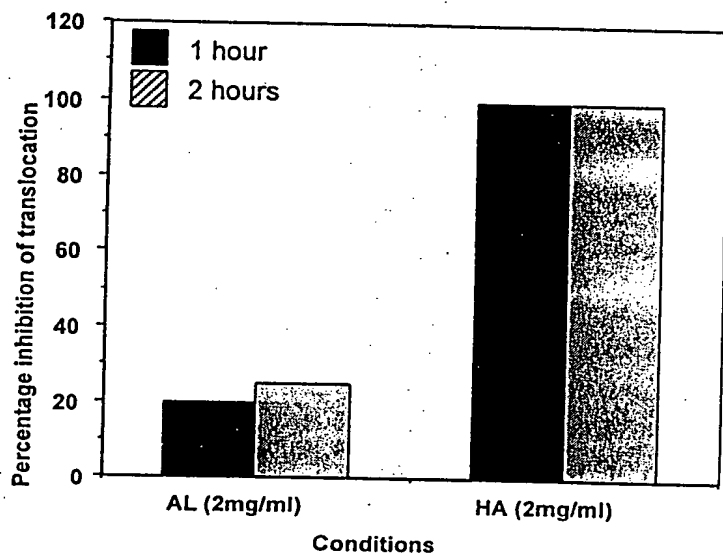


Fig. 9

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~~Figure 9~~





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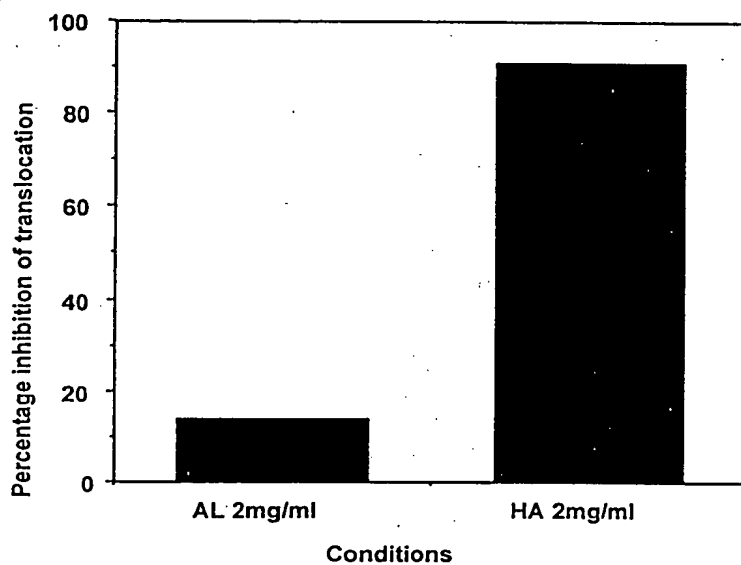


Fig. 10

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~~Figure 10~~



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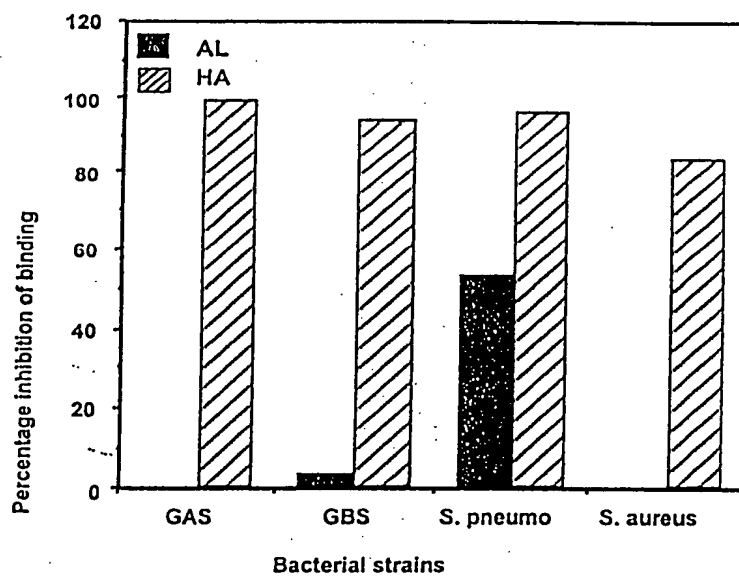
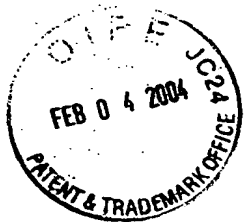


Fig. 11

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~~Figure 11~~



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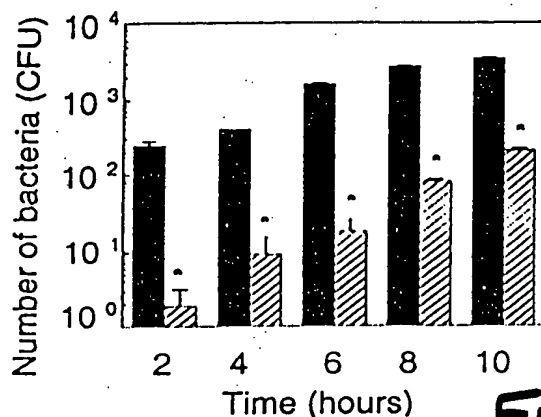


Fig. 12A

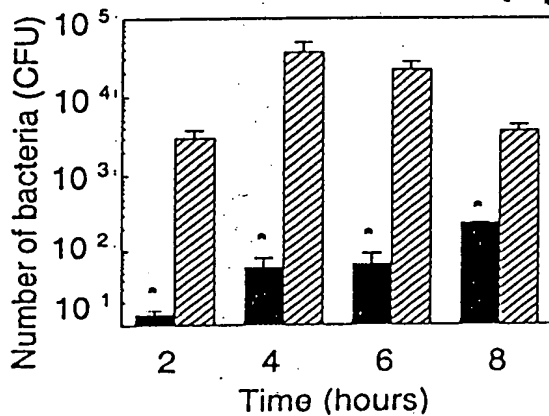


Fig. 12B

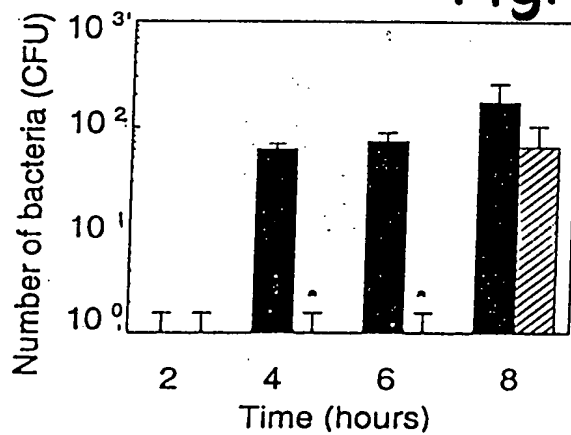


Fig. 12C

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~~Figure 12~~



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~~A~~

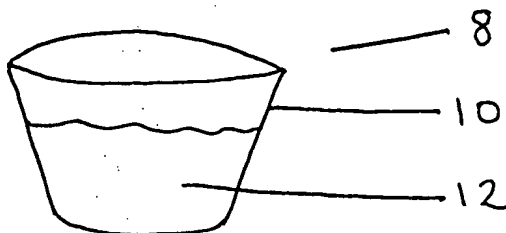


Fig. 13A

~~B~~

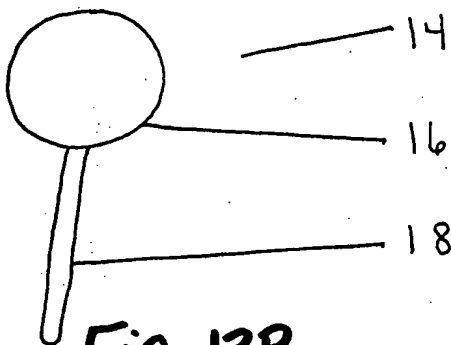


Fig. 13B

~~C~~

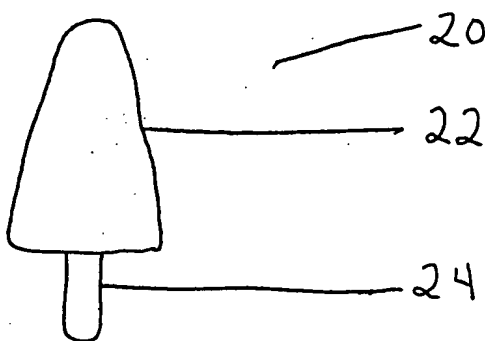


Fig. 13C

~~D~~



Fig. 13D

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~~Figure 13~~